

ganized medicine) are very considerable. This cannot be accomplished by force. It is a problem for the intellect.

The California Medical Association has made a small beginning with its "troika" of planning committees and its recent emphasis on planning and goals. Once the problem is clearly in mind, perhaps physicians can devise an organizational "organism" which will be parabiological in the sense that it will have many of the characteristics of the human organisms of which it is composed, organisms which are at once so general in purpose and yet so easily adaptable to environmental change, often accomplishing this adaptation by modifying the environment itself.

Cancer and the Nervous System

METASTASIS OF CANCER to the central nervous system is well known, but in the past 20 years there has been growing recognition of a group of central and peripheral nervous disorders in cancer, not caused by direct tumor involvement. It has been exciting to neurologists to witness the emergence of a large new class of neurological diseases, but the importance of these diseases lies in their usefulness in diagnosing cancer, as well as the insight they may offer into the pathogenesis of "degenerative" diseases of the nervous system. Some of the remote effects of tumors on other organs are now known to be caused by abnormal production of substances similar or identical to natural hormones. The neurological syndromes, however, are largely unexplained.

The remote effects of cancer on the nervous system can be grouped into two broad categories. On the one hand there are metabolic effects of systemic disturbances like hypercalcemia or hyponatremia; infection by organisms, such as yeast or fungi, to which cancer patients are particularly but not uniquely susceptible; and vascular accidents, such as occur in leukemia and altered clotting states. On the other hand is a group of degenerative or inflammatory diseases of more or less unknown etiologic lineage, some of them seen almost exclusively in association with malignant tumors. Elsewhere in this issue, Rubinstein has thoroughly reviewed the clinical features of the latter group, and his report makes apparent the heavy contributions of English neurologists to this

subject, especially the late Lord Brain, P. B. Croft, and Marcia Wilkinson. Despite their efforts, however, classification of these disorders (which they have called "carcinomatous neuromyopathy") still presents difficulties. Not all would agree, for instance, that classical amyotrophic lateral sclerosis occurs with increased frequency in cancer, as claimed by Brain, Croft, and Wilkinson and by Norris and Engel. Certain other spinal cord syndromes in cancer are also not firmly established.

The syndromes which are now widely accepted include: (1) progressive multifocal leukoencephalopathy, a cerebral and rarely spinal demyelinating disease with unique pathological features, occurring mainly in leukemia and lymphoma but also in other cancers and chronic diseases; (2) diffuse polioencephalopathy, characterized by neuronal degeneration in many parts of the neuraxis, and presenting with symptoms of dementia, cerebellar deficit, bulbar palsy, lower motor neuron disease, sensory neuropathy or a mixture of several of these; (3) mixed sensorimotor neuropathy due primarily to segmental demyelination of peripheral nerves; (4) the myasthenic syndrome of Eaton and Lambert, a defect of neuromuscular transmission characterized by paradoxical increase of strength during voluntary effort; and (5) myopathy, including polymyositis and dermatomyositis. It is not uncommon for some of these types to co-exist, adding to the difficulties of classification and diagnosis. This is especially true of the neuromuscular syndromes (which account for more than two-thirds of the cases) in which neuropathy and myopathy may both be present. For this reason some authors, perhaps prematurely, have abandoned distinctions between neurogenic and myogenic weakness in cancer.

How frequent is non-metastatic as compared with the frequency of metastatic disease in cancer? It is surprisingly difficult to discover the incidence of either complication. Metastasis to the brain was formerly said to be observed in 5 percent of cancer patients at autopsy, but more recently figures of 35 percent¹ and 17 percent² have been reported (the higher figure includes metastasis within the spinal canal). The only information about the incidence of non-metastatic neurological syndromes comes from Croft and Wilkinson's³ survey of 1,476 living patients with carcinoma. Seven percent of these patients had clinical evidence of "carcinomatous neuromyopathy," the large majority belonging to the "neuromuscular" type —

proximal weakness, muscle atrophy and loss of reflexes. It is not clear, in the absence of pathological verification, how many of these findings were actually due to carcinomatous neuromyopathy. (Of control patients, 11 percent had some neurological findings.) However, the incidence varied widely with the type of cancer (ranging from 0.5 percent for rectum to 16 percent for ovary or lung), a fact which lends some validity to the diagnoses. Furthermore, in carcinoma of lung and breast the incidence of clinically evident metastatic and non-metastatic complications was about the same — 16 percent. Clearly, however, an autopsy series will be necessary to establish the true incidence of these disorders. On clinical grounds alone, it is quite possible to mistake metastatic for non-metastatic brain disease, and neuropathy may be simulated by meningeal invasion of nerve roots by tumor.

In the case of leukemia and lymphoma, neurological complications are common but are rarely due to progressive multifocal leukoencephalopathy or other neuromyopathy. Spinal cord compression by extradural tumor is the commonest complication of lymphoma. Intracerebral hemorrhage is an important complication of leukemia, and leukemic meningitis is being seen more and more, especially in blastic leukemia, a change attributable to prolonged survival of patients treated with antileukemic drugs which do not enter the nervous system. Infection by yeast, fungi, cytomegalovirus, and other organisms is a constant danger, especially when immunosuppressive agents are used.

The non-metastatic syndromes have one feature of major importance. Except for progressive multifocal leukoencephalopathy they often appear months or years before the underlying malignancy is apparent, and this can alert the clinician to search diligently for the responsible neoplasm. This sequence of diagnosis is already well established in neurological practice and in some cases has led to cure of the malignant lesion. The neuromyopathy itself may improve with treatment of the underlying cancer, but this effect has not been consistent.

The causes of these remarkable diseases may well be diverse. In progressive multifocal leukoencephalopathy the constant finding of intranuclear inclusions in oligodendroglia (the central nervous system cells responsible for formation and maintenance of myelin) early suggested a viral cause. This view has now been strongly supported by

electron micrographs from several laboratories showing intranuclear crystalline arrays in oligodendroglia that closely resemble polyoma virus of the papova group.⁴ At the other end of the nervous system, Chou^{5,6} has reported electron microscopic evidence of particles resembling myxovirus and picornavirus in the muscles of patients with polymyositis and dermatomyositis, though none of the patients had cancer. This preliminary finding is particularly interesting because these myopathic conditions have commonly been attributed to autoimmune processes. Hypersensitivity has also been invoked to explain the rare ganglioradicular sensory neuropathy in cancer, since serum from four such patients was found to contain antibodies reacting with nerve cells.⁷ Lymphocytic infiltration and perivascular cuffing have been variably noted in the diffuse polioencephalopathy syndromes, including sensory neuropathy, and a viral cause must still be considered for this group. In recent years, scrapie in animals and kuru and Creutzfeldt-Jakob disease in man, disorders once classified as degenerative and even hereditary, have been transmitted to animals by inoculation of pathological material.⁸ Gajdusek and his coworkers⁸ at the National Institutes of Health are now investigating other "degenerative" diseases of the nervous system by similar techniques. The studies are slow and expensive, and common diseases like amyotrophic lateral sclerosis and the presenile dementias take precedence, but perhaps these techniques can eventually be used to elucidate the non-metastatic neurological syndromes in cancer.

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REFERENCES

1. Lesse, S., and Netsky, M. G.: Metastasis of neoplasms to central nervous system and meninges, *Arch. Neurol. Psychiat.*, 72:133, 1954.
2. Aronson, S. M., Garcia, J. H., and Aronson, B. E.: Metastatic neoplasms of the brain: Their frequency in relation to age, *Cancer*, 17:558, 1964.
3. Croft, P. B., and Wilkinson, M.: The incidence of carcinomatous neuromyopathy with special reference to carcinoma of the lung and the breast: *In* Remote Effects of Cancer on the Nervous System, Edited by Lord Brain and F. Norris, Jr., Grune and Stratton, Inc., New York-London, 1965.
4. Woodhouse, M. A., Dayan, M. A., Burston, J., Caldwell, I., Adams, J. H., Milcher, D., and Urich, H.: Progressive multi-focal leukoencephalopathy; electron microscope study of four cases, *Brain*, 90:863, 1967.
5. Chou, S.-M.: Myxovirus-like structures in a case of human chronic polymyositis, *Science*, 158:1453, 1967.
6. Chou, S.-M., and Gutmann, L.: Picornavirus-like crystals in subacute polymyositis, *Neurology*, 19:286, 1969.
7. Wilkinson, P. C., and Zeromski, J.: Immunofluorescent detection of antibodies against neurones in sensory carcinomatous neuropathy, *Brain*, 88:529, 1965.
8. Gibbs, C. J., and Gajdusek, D. C.: Kuru—a prototype subacute infectious disease of the nervous system as a model for the study of amyotrophic lateral sclerosis; *In* Motor Neuron Diseases: Research on Amyotrophic Lateral Sclerosis and Related Disorders, Edited by F. H. Norris, Jr., and L. T. Kurland, Grune & Stratton, Inc., New York, 1969.